

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 16090

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

15 FEB 2005 / 15 JAN 2006

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2005/007702

International filing date (day/month/year)
09.03.2005

Priority date (day/month/year)
15.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D209/08, C07D409/12, C07D405/12, A61K31/4045, A61P3/04, A61P3/10, A61P25/24, A61P25/28,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007702

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 18-22

because:

- ☒ the said international application, or the said claims Nos. 18-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007702

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	17, 19-23
	No: Claims	1-16, 18
Inventive step (IS)	Yes: Claims	1-23
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-17, 23
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for these claims (Article 34(4)(a)(i) PCT).

The scope of the claim set is unclear within the meaning of Article 6 PCT due to the term "prodrugs" in claims 1 and 2. Potential "prodrugs" of the compounds of formula (I) and (II) (e.g. esters or amides) are so widely known that it is not possible to cite all documents relevant to the issue of novelty. D3 and D4 have been cited as exemplary documents disclosing potential "prodrugs" of the structurally defined compounds of the present invention.

n is not defined in claim 1. For the search it has been assumed that n is for claim 1 as it is defined in claim 2, i.e. n=1-3. It is noted that compounds wherein n=0, i.e. e.g. $R1=C(O)R8$ or $C(O)OR8$, are widely known (e.g. from D3 and D4).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: WO 03/101963 A (ELI LILLY) 11 December 2003 (2003-12-11)

D2: WO 02/051805 A (BAYER) 4 July 2002 (2002-07-04)

D3: YEE ET AL: "A novel series of selective leukotriene antagonists: exploration and optimization of the acidic region in 1,6-disubstituted indoles and indazoles" JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 9, 1990, pages 2437-2451, XP002332451

D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1996, RAFALSKI, M. ET AL: "Synthesis and biological evaluation of substituted benzimidazoles - potential GPIIb/IIIa receptor antagonists" XP002332455 retrieved from STN Database accession no. 1996:696065

Novelty (Article 33(2) PCT)

Since the present claim set encompasses "prodrugs" of the structurally defined compounds of the formulae I and II, claims 1-16 and 18 are not novel in view of D3 and D4, as the compounds disclosed therein are e.g. amides of the present compounds which can be hydrolysed in vivo to compounds of the present invention.

The present compounds differ from the compounds in D1 in the benzofused heterocyclic structure and from the compounds in D2 in that the benzofused heterocycle is linked at its 1-position with the second cycle.

Inventive Step (Article 33(3) PCT)

D1 discloses opioid receptor antagonists and D2 discloses compounds for the treatment of e.g. obesity. D1 can be regarded as the closest prior art.

The problem of the present invention was the provision of new opioid receptor antagonists for the treatment of e.g. obesity.

The present compounds are structurally unrelated with the compounds of D1 and the position of the linkage between the benzofused heterocycle and the second cycle is not suggested by D2 and/or D1. D3 and D4 disclose compounds with a different pharmacology and medical uses.

The present invention is therefore based on an inventive step.

Clarity (Article 6 PCT)

- The variable "n" is not defined in claim 1.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/007702

- The claims 17-19 and 21-23 lack a reference to claim 1.
- There is a mistake in the numbering of the claims: two claims have been numbered "18".
- Due to the term "prodrugs" the scope of the claim set is not clearly defined.